REMARKS

Reconsideration of this application is respectfully requested.

DOUBLE PATENTING REJECTIONS

Claims 163 and 170 were rejected under the judicially created doctrine of obviousness-type double patenting as being obvious over claims 1, 2, 11, and 12 of U.S. Patent No. 7,232,938; claims 1-9, 11-20, and 22 of U.S. Patent No. 7,304,204; claims 17 and 18 of U.S. Patent No. 7,307,198; claims 1-3 and 10 of U.S. Patent No. 7,321,076; claims 1, 2, 7-9, 14, and 19; of U.S. Patent No. 7,326,824; claims 1, 6-11, and 16-20 of U.S. Patent No. 7,326,825; claims 12 and 14 of U.S. Patent No. 7,332,648; claims 1, 6-11, and 16-20 of U.S. Patent No. 7,355,094; and claims 17-32 of U.S. Patent No. 7,361,804. Solely to expedite prosecution of this application, and not in acquiescence to the propriety of this rejection, Applicant submits herewith Terminal Disclaimers over U.S. Patent Nos. 7,232,938; 7,304,204; 7,307,198; 7,321,076; 7,326,824; 7,326,825; 7,332,648; 7,355,094; and. 7,361,804. Accordingly, this rejection has been obviated.

Claims 163 and 170 were rejected under the judicially created doctrine of obviousness-type double patenting as being obvious over claims 27, 32-34, 43, and 48-50 of U.S. Application No. 11/543,786 and claims 19, 24-26, 35, and 40-42 of U.S. Application No. 11/544,038. Since the claims have not been patented, these rejections are ***provisional***. (Office Action at 6.) Applicant requests that the rejection be held in abeyance until indication of allowable subject matter in these applications.

Claims 163 and 168-171 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being obvious over claims 40-55 of

U.S. Application No. 11/068,903. Solely to expedite prosecution of this application, and not in acquiescence to the propriety of this rejection, Applicant submits herewith a Terminal Disclaimer over U.S. Application No. 11/068,903, now U.S. Patent 7,432,415.

REJECTIONS UNDER 35 U.S.C. § 101

Claims 163 and 168-171 were rejected under 35 U.S.C. § 101, as allegedly being directed to non-statutory subject matter. The Examiner alleges that the claimed mammals are a "product of nature." (Office Action at 8.) The Examiner concedes that Applicant's claimed mammals require the hand of man. (Office Action at 7.) Nonetheless, the Examiner contends that the surrogate female actually "makes" the cloned mammal. (Id.) The Examiner alleges that by virtue of employing a naturally occurring female to produce the clone, Applicant's clone is a product of nature. (Id.) The Examiner concedes that Applicant's clone and the donor animal will have differences. (Id. at 10.) Nevertheless, the Examiner contends that these differences do not make Applicant's clone "new." (Id.)

Applicant traverses the rejection. Mammals do not naturally reproduce by cloning. Thus, a cloned mammal covered by Applicant's claims is a non-naturally occurring product of human ingenuity. Consequently, Applicant is not claiming a product of nature, but one that is made by man. These facts are sufficient for Applicant's claims to fulfill the requirements of 35 U.S.C. § 101.

The Examiner's allegation that Applicant's clones are products of nature because a naturally occurring female was employed to make the clone is in error. If this were true, many, if not all, recombinant biological products would be considered "products of nature." For example, under the Examiner's reasoning, any recombinant drug that

employed bacteria to "make" it would be a "product of nature." Certainly, this is not the law.

As the Supreme Court held in *Diamond v. Chakrabarty*, statutory subject matter includes "anything under the sun that is made by man." 447 U. S. 303, 308 (1980). The relevant distinction between non-statutory and statutory subject matter is between products of nature, whether living or not, and human-made inventions. *Id*. at 313. Since clones of mammals are not products of nature, but are human-made inventions, the requirements of 35 U.S.C. § 101 are fulfilled by Applicant's claims.

Moreover, whether Applicant's invention is "new" is not relevant to an analysis of whether Applicant is claiming statutory subject matter under 35 U.S.C. § 101. As stated in a recent *en banc* decision from the Federal Circuit, *In re Bilski*, 545 F.3d 943 (2008):

> Although § 101 refers to "new and useful" processes, it is overall "a general statement of the type of subject matter that is eligible for patent protection 'subject to the conditions and requirements of this title.'" Diehr, 450 U.S. at 189 (quoting § 101). As the legislative history of § 101 indicates, Congress did not intend the "new and useful" language of § 101 to constitute an independent requirement of novelty or non-obviousness distinct from the more specific and detailed requirements of §§ 102 and 103, respectively. Diehr, 450 U.S. at 190-91. So here, it is irrelevant to the § 101 analysis whether Applicants' claimed process is novel or non-obvious.

Furthermore, the Examiner admitted that the clone and the donor animal will have differences. (Office Action at 10.) To the extent that 35 U.S.C § 101 requires an invention to be "new," Applicant traverses for the reasons set for in the response filed March 30, 2008. As previously set forth, these differences are sufficient to make Applicant's invention new.

In addition, as previously set forth, anticipation under 35 U.S.C § 102 can be found only when the reference discloses ***exactly*** what is claimed; where there are

differences between the reference disclosure and the claim, the rejection must be based on 35 U.S.C § 103, which takes differences into account. *Titanium Metals Corp. v. Banner*, 227 USPQ2d 773, 777 (Fed. Cir. 1985). Thus, anticipation is not shown by a prior art disclosure which is only "substantially the same" as the claimed invention. *Jamesbury Corp. v. Litton Industrial Products, Inc.*, 225 USPQ 253, 256 (Fed. Cir. 1985). Rather, the ***identical*** invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Following legal precedent, the fact that the clone and its parent are different, which the Examiner concedes, precludes anticipation of Applicant's claims. As explained by the Court of Appeals for the Federal Circuit in overturning an anticipation rejection where there were differences between the claims and the prior art:

> The opinion says anticipation may be shown by less than "complete anticipation" if one of ordinary skill may in reliance on the prior art "complete the work required for the invention", and that "it is sufficient for an anticipation 'if the general aspects are the same and the differences in minor matters is only such as would suggest itself to one of ordinary skill in the art.'" Those statements relate to obviousness, not anticipation. Anticipation requires the presence in a single prior art disclosure of all elements of a claimed invention arranged as in the claim. *Soundscriber Corp. v. U.S.*, 360 F.2d 954, 960, 148 USPQ 298, 301 (Ct. Cl. 1966). A prior art disclosure that "almost" meets that standard may render the claim invalid under §103; it does not "anticipate."

Connell et al. v. Sears, Roebuck & Co., 220 USPQ 193, 198 (1983).

Legal precedent clearly dictates that any difference, trivial or otherwise, precludes anticipation. See *Connell,* 220 USPQ at 198. Any differences must be assessed under an obviousness analysis, which should have no relevance to whether Applicant's clones are patentable subject matter under 35 U.S.C. § 101.

Pending claims 163 and 168-171 recite that the mammal is a **clone** of a pre-existing, non-embryonic donor mammal. It is irrefutable that nature does not make **clones**. Since clones of pre-existing mammals do not exist in nature, Applicant's clones are statutory subject matter.

REJECTIONS UNDER 35 U.S.C. §§ 102/103

The Examiner rejected claims 163 and 168-171 under 35 U.S.C. § 102 or § 103 as being anticipated by or obvious over a number of references teaching mice, rabbits, horses, and rats produced by *in vitro* fertilization. Applicant traverses the rejection.

Anticipation under 35 U.S.C § 102 can be found only when the reference discloses exactly what is claimed. *Titanium*, 227 USPQ2d at 777. The identical invention must be shown in as complete detail as is contained in the patent claim. *Richardson v. Suzuki Motor Co*., 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Thus, anticipation requires the presence in a single prior art disclosure of all elements of a claimed invention. *Connell*, 220 USPQ at 198.

The cited references do not disclose exactly what is claimed. Rather, the cited references are missing an element recited in Applicant's claims. The cited prior art references do not disclose **a clone**. This limitation of Applicant's claim precludes Applicant's clone from being anticipated by the cited references. See *Connell*, 220 USPQ at 198. The Examiner interprets Applicant's claims as follows: "The phrase 'live born clone of a . . . mammal' imbues the method by which the clone was made, nuclear transfer." (Office Action at 26.) Applicant disagrees. Applicant's claims 163 and 168-171 are not product-by-process claims and are not limited to any particular method.

The references cited by the Office each describes mammals made by in vitro fertilization procedures. Thus, the mammals produced in these references were generated by using an egg and a sperm, albeit using *in vitro* procedures. The mammals made in these references were not clones of either of these parental mammals, since sexual reproduction was used to generate the embryos used in the IVF procedures. Rather, these mammals generated by IVF would have been a mixture of the genetic complement of their two parents, and thus the mammals would not have had the same genetic complement as either of the parents. Thus, these mammals were not identical to either of its parents, but only 50% identical to each of them. Consequently, the mammals generated by the *in vitro* fertilization procedures of the cited references were not a live-born ***clone*** of a pre-existing, non-embryonic, donor mammal. The cited prior art references lack this element of Applicant's claims.

A live-born clone of a pre-existing, non-embryonic, donor mammal as claimed is a time-delayed, inexact copy of a non-embryonic mammal. The claimed clone requires two animals, namely, a pre-existing, non-embryonic, parental mammal and a clone of that parental mammal. The cited references did not generate such a pair of mammals. In none of the cited references did a pre-existing, non-embryonic, parental mammal and a clone of that parental mammal exist. The prior art references lack this requirement of Applicant's claims.

Thus, Applicant's clones differ in many ways from the mammals of the cited references. These differences preclude a finding of anticipation of Applicant's claims. *See Titanium*, 227 USPQ2d at 777.

The differences between Applicant's clones and the mammals of the cited references also preclude a finding of obviousness of Applicant's claims. As explained in M.P.E.P. § 2141.02:

> In determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the invention as a whole would have been obvious. *Stratoflex, Inc. v Aeriquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed Cir. 1983); *Schneck v. Norton Corp.*, 713 F.2d 782, 218 USPQ 698 (Fed Cir. 1983).

A live-born clone of a pre-existing, non-embryonic, donor mammal as claimed is not taught or suggested by the cited references. Prior to Applicant's invention, the generation of a live-born clone of a pre-existing, non-embryonic, donor mammal would have been expected to be impossible. Since there must be a reasonable expectation of success to support a conclusion of obviousness, what was thought to be impossible cannot be obvious. *See, e.g., In re Rinehart*, 189 USPQ 143 (CCPA 1976). Accordingly, Applicant respectfully requests withdrawal of the rejection.

Applicant points out that the previous Board Decision in this application concluded that Applicant's claims to horses and rats were not anticipated or obvious over other previously cited references, stating: "The Examiner has not relied on any evidence that a horse or rat having the same nuclear genetic code as a previously existing horse or rat existed or was enabled prior to Campbell's disclosure." (Decision at 28.) The same is true here. None of the cited references show that a horse or rat having the same nuclear genetic code as a previously existing horse or rat existed or was enabled prior to Campbell's disclosure. Accordingly, Applicant respectfully submits that the rejection is in error and should be withdrawn.

The Examiner further questions: "If we have two rabbits, what test does one use to tell which one is produced by nuclear transfer as presently claimed, that is a cloned rabbit, from the rabbit produced by IVF?" (Office Action at 30.) First, this is a question relevant to infringement, not one of anticipation or obviousness. Second, Applicant's claims are not product-by-process claims. Thus, they do not require that the clone is "produced by nuclear transfer," but only that it is a clone. Third, one skilled in the art could readily determine which animal was a clone by comparing the DNA of the progeny to the parent animals. Only the clone would have the same genetic complement as its parent, i.e., the nuclear donor. The IVF produced mammal would have a mixture of the genetic complement of its egg donor and sperm donor. This could readily be determined by DNA analysis using routine techniques in the art.

REJECTIONS UNDER 35 U.S.C. § 112

The Examiner rejected claims 163 and 168-171 under 35 U.S.C. § 112, first paragraph, as lacking an enabling disclosure. Applicant traverses the rejection for the reasons set forth in the response filed March 30, 2008.

In addition, Applicant questions the Examiner's rejection of Applicant's claims for both lack of enablement and being anticipated or obvious over the prior art. Applicant submits that that these rejections are inconsistent with each other. The Examiner must apply the law consistently to each application after considering all the relevant facts. M.P.E.P. § 2144(III). Applicant requests clarification as to why Applicant's claimed invention is allegedly not enabled if the prior art allegedly provides an enabling disclosure sufficient to make the claimed invention anticipated or obvious.

Successful Cloning of Mice

The Examiner contends that the method used in cloning mice included a prolonged interval between nuclear injection and oocytes activation, suppressing cytokeneisis. (Office Action at 15.) Applicants traverse the rejection for the reasons set forth in the response filed March 30, 2008.

As previously detailed by Applicant, Wakayama's delayed activation procedure is described in Applicant's specification. In contrast to the Examiner's contentions otherwise, Applicant's specification does not state that "the reconstructed embryo needs to be incubated in the presence of a microtubule destabilizer." (Office Action at 20.) This is simply one embodiment of Applicant's invention. Moreover, the Examiner's comments regarding Wakayama et al. relating to clones made from ES cells refers to a different article by Wakayama et al. in 1999. In 1998, in *Nature*, Jul 23:369-74, Wakayama et al. reports the successful cloning of mice using somatic cells. Thus, the conclusion of Ogura et al. (2000) that only delayed activation is important for cloning mice refers to cloning mice with **somatic cells**.

Furthermore, just because a particular technique was successful in cloning mice, does not mean that this technique is required or that other techniques will not work. Accordingly, Applicant respectfully requests withdrawal of the rejection.

Successful Cloning of Rabbits

The Examiner contends that the cloning of rabbits was only successful when surrogate females were asynchronous by 22 hours from the recipient oocytes. (Office

Action at 14.) Applicants traverse the rejection for the reasons set forth in the response filed March 30, 2008.

As previously set forth, Landa (1981) and Al-Hasani et al. (1986) teach that using asynchronous transfer for *in vitro* manipulated rabbit embryos is beneficial. Accordingly, the skilled artisan would have considered the work of important with respect to *in vitro* manipulated rabbit embryos. Having read these articles, the skilled artisan would have known that using asynchronous transfer for reconstructed rabbit nuclear transfer embryos would be beneficial since reconstructed rabbit nuclear transfer embryos are *in vitro* manipulated embryos. The fact that cloning and IVF are materially different techniques does not negate this.

Furthermore, just because a particular technique was successful in cloning rabbits, does not mean that this technique is required or that other techniques will not work. Accordingly, Applicant respectfully requests withdrawal of the rejection.

Successful Cloning of Rats

The Examiner contends that the cloning of rats required the use of a protease inhibitor to address the rapid activation of rat oocytes. (Office Action at 14.) Applicants traverse the rejection for the reasons set forth in the response filed March 30, 2008.

As previously set forth, the problem and the solution to spontaneous activation of rat oocytes were well-known in the art. Keefer et al. (1982) reported a problem with rat oocytes, namely, that ovulated rat oocytes activated spontaneously during *in vitro* culture. (At 371, Abstract.) Only 1.3% of rat oocytes remained in metaphase II after *in vitro* culture for 4-5 hours. (*Id*. at 373, Table 1.) Moreover, spontaneous activation of

rat oocytes was completed within 90 minutes during *in vitro* culture. (*Id*. at 376-377, bridging paragraph.)

Keefer et al. (1982) also provided a solution to this problem. 98% of rat oocytes remained in metaphase II after *in vitro* culture for 10 minutes, but only 24% after *in vitro* culture for 25 minutes. (*Id*. at 371, abstract.) Moreover, nearly 75% of rat oocytes remained in metaphase II after *in vitro* culture for 4-5 hours when removed and cultured as rapidly as possible. (*Id*.)

Based on the Campbell '862 application and Keefer et al., it would have been understood in February of 1997 that to obtain rat oocytes in the metaphase II phase of the cell cycle for nuclear transfer, one should try to avoid spontaneous activation of the rat oocytes. Moreover, based on Keefer et al. (1982), it would have been understood that rat oocytes should be removed and cultured as rapidly as possible to avoid spontaneous activation.

Furthermore, just because a particular technique was successful in cloning rats, does not mean that this technique is required or that other techniques will not work. Accordingly, Applicant respectfully requests withdrawal of the rejection.

Successful Cloning of Horses

The Examiner contends that the cloning of horses was aided by advances in assisted reproduction in the horse, including oocyte activation, inhibition of protein synthesis and protein phosphorylation, and zona-free manipulation. (Office Action at 14.) Applicants traverse the rejection for the reasons set forth in the response filed March 30, 2008.

The availability of oocytes appears to be a major factor in horse cloning. Lagutina et al. (2005), a copy of which is provided herewith, states: "In horse nuclear transfer, the availability of horse oocytes is a limiting factor due to the anatomy and physiology of the mare's ovary which makes this species a poor oocyte donor compared with other large domestic species." (At 560, col. 1, first full paragraph.) Lagutina et al. (2005) further states: "The objectives of our research concentrate on the optimization of the nuclear transfer procedure to make efficient use of the limited numbers of oocytes available in this species." (At 560, col. 1, second paragraph.)

In order to perform nuclear transfer in horses, a source of a large number of horse oocytes is a facilitating factor. That is, the larger the number of oocytes one starts with, the higher the chances of successful generation of cloned horses. However, the low availability of horse oocytes does not equate with a lack of enablement.

Moreover, neither inhibiting both protein synthesis and phosphorylation at the oocyte activation stage nor using a zona-free manipulation technique is critical for cloning horses. First, inhibiting both protein synthesis and phosphorylation at the oocyte activation stage is not critical to successfully clone horses. Hinrichs et al. (1995), a copy of which is provided herewith, indicates that the combination of a calcium ionophore with cycloheximide (CHX), a protein synthesis inhibitor, resulted in 49% activation of equine oocytes. (At 324, first full paragraph.) This experiment was performed *in the absence of any phosphorylation inhibitor*. Thus, it was well-known prior to February of 1997 that the combination of a calcium ionophore with a protein synthesis inhibitor was sufficient for activating horse oocytes. Based on Hinrichs et al. (1995), it would have been expected in February of 1997 that the combination of

calcium ionophore with CHX would serve as to activate nearly half of the equine oocytes exposed to this activation protocol, *in the absence of any phosphorylation inhibitor*. This activation procedure would have been expected to be sufficient to clone horses by somatic cell nuclear transfer in February of 1997.

Likewise, Lazzari et al. (2002) indicates that, for equine oocytes, the activation rate was 30.6% for ionomycin (a calcium ionophore) and CHX (a protein synthesis inhibitor) alone, 60% for ionomycin and 6-dimethylaminopurine (6-DMAP), a phosphorylation inhibitor, and 93.1% for ionomycin and CHX + DMAP. Thus, the activation of equine oocytes in Lazzari et al. (2002) was successful when oocytes were activated first with ionomycin, a calcium ionophore, and second with a protein synthesis inhibitor alone (as previously taught by Hinrichs et al. (1995)), a phosphorylation inhibitor alone, or with both a protein synthesis inhibitor and a phosphorylation inhibitor. All of these combinations were successful in activating horse oocytes. Although use of a calcium ionophore with both a protein synthesis inhibitor and a phosphorylation inhibitor was 3-fold better than a calcium ionophore with the protein synthesis inhibitor alone in this experiment, a calcium ionophore with a protein synthesis inhibitor was still sufficient for activating horse oocytes, albeit at 3-fold less efficiency than when combined with a phosphorylation inhibitor. Clearly, although a phosphorylation inhibitor may increase the efficiency of horse cloning, it is not critical.

Moreover, it would not have been expected that it was necessary to increase the activation rate to 93.1%, in order to achieve success. Although an increase in activation rates might be expected to increase the efficiency of cloning somewhat, the efficiency

could also be increased by simply increasing, for example doubling, the number of nuclear transfer oocytes.

Second, the zona-free manipulation technique is not critical to successfully clone horses. Lagutina et al. (2005) found that the "zona-free method for embryo reconstruction proved very efficient in increasing the fusion rate and the efficient use of oocytes." (At 565-566, bridging paragraph.) Specifically, Lagutina et al. (2005) found that "the zona-free method is about 3.2 times more efficient than the zona-enclosed method in the case of cumulus-derived NT-embryos and 2.3 times more effective in the case of fibroblast-derived NT-embryos." (At 561-562, bridging paragraph.) Although the zona-free method may increase the efficiency of horse cloning, it clearly is not critical.

As further evidence that the zona-free method is not required to clone horses, Woods et al. (2003) reports the cloning of a mule using horse oocytes. (At 1063, col. 1-2, bridging paragraph.) Woods et al. (2003) used oocytes with an intact zona. (Woods et al. (2003), Supporting Online Material at 3.) Since Woods et al. (2003) did not use the "zona-free" method, it is not critical for horse cloning.

Based on Woods et al. (2003) and Lagutina et al. (2005), the "zona-free" method is not required for cloning horses by somatic cell nuclear transfer. While it may increase the efficient utilization of oocytes, the use of more oocytes can compensate for this increase.

Furthermore, just because a particular technique was successful in cloning horses, does not mean that this technique is required or that other techniques will not work. Accordingly, Applicant respectfully requests withdrawal of the rejection.

Conclusion

The Examiner's arguments are based on the ***successful*** cloning of the claimed species with procedures that may include additional, non-critical, variations of Campbell's procedures. This simply means that variations of Campbell's teachings are successful in cloning mammals. This does not mean that Campbell's teachings are insufficient.

Moreover, many of the variations used in the cited articles to appear to involve simply applying well-known techniques for oocyte and embryo manipulation to cloning methodologies. For example, cloning rabbits appears to have involved little more than applying well-known techniques for *in vitro* manipulated rabbit embryos. Also, cloning of rats appears to have involved little more than applying well-known techniques for harvesting unactivated metaphase II rat oocytes. The successful cloning of a mammal using a variation of Campbell's technique cannot negate enablement. Such results do not indicate that the employment of Campbell's technique was not routine.

The mere repetition of a cloning procedure does not equate with undue experimentation. *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (1988). If all that is required for success is mere repetition of the disclosed process, Applicant's claims cannot require undue experimentation.

Applicant submits that this application is in condition for allowance. Should the Examiner disagree, she is invited to contact the undersigned to discuss any outstanding issues.

Respectfully submitted,

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Dated: May 25,2009

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